Title: Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Running Title: Egg Consumption and Risk of Cardiovascular Outcomes

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Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association
ABSTRACT

Introduction: Considerable controversy remains on the relationship between egg consumption and cardiovascular disease risk. The objective of this systematic review and meta-analysis was to explore the association between egg consumption and overall cardiovascular disease events.

Methods: We systematically searched Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception from 1966 through January 2020 for observational studies that reported the association between egg consumption and cardiovascular disease events. Two investigators independently reviewed data. Conflicts were resolved through consensus. Random-effects meta-analyses were used. Sources of heterogeneity were analyzed.

Results: We identified 23 prospective studies with a median follow-up of 12.28 years. A total of 1,415,839 individuals with a total of 123,660 cases and 157,324 cardiovascular disease events were included. Compared to the consumption of no or 1 egg/day, higher egg consumption (more than 1 egg/day) was not associated with significantly increased risk of overall cardiovascular disease events (pooled hazard ratios, 0.99; 95% CI, 0.93-1.06; p<0.001; I² = 72.1%). Higher egg consumption (more than 1 egg/day) was associated with a significantly decreased risk of coronary artery disease (pooled hazard ratios, 0.89; 95% CI, 0.86-0.93; p<0.001; I² = 0%), compared to consumption of no or 1 egg/day.

Conclusions: Our analysis suggests that higher consumption of eggs (more than 1 egg/day) was not associated with increased risk of cardiovascular disease, but associated with a significant reduction in risk of coronary artery disease.
Clinical Significance

- Consumption of more than one egg per day was not associated with an increased risk of cardiovascular disease.
- Consumption of more than one egg per day was associated with a reduction in the risk of coronary artery disease.
- Consumption of more than one egg per day was not associated with an increased risk of stroke.

INTRODUCTION

Eggs are a nutrient-dense (e.g., minerals, folate, B vitamins, and fat-soluble vitamins), a rich source of bioactive compounds (e.g., lutein and zeaxanthin) and high-quality protein. (1) Nutrients and bioactive compounds in eggs may theoretically contribute to improving cardiovascular disease. (2) However, eggs are also high in cholesterol, and, for example, one large egg contains approximately 186 mg of cholesterol. Although no direct evidence that egg consumption can lead to elevated cholesterol levels, the American Heart Association (AHA) Dietary Guidelines Revision 2000 has recommended the public to consume less than 300 mg/day of cholesterol to minimize the elevation of blood cholesterol. (3) Interestingly, the more recent Dietary Guidelines for Americans 2015–2020, has no longer provide limits on egg intake but recommended egg intake as healthy eating patterns. (4) Previous studies have been demonstrated inconsistent results of associations of egg consumption with cardiovascular disease, leading to considerable controversy. (5-8) To date, previous studies on egg consumption and cardiovascular disease risk have been inconclusive. The objective of this systematic review and meta-analysis
was to explore the association between egg consumption and cardiovascular disease.

**METHODS**

**Search strategy**

We developed search strategies for Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception to January 2020. The search strategies were peer-reviewed by experienced librarians. The language or date of publication was not limited. The strategies included MeSH and Embase terms as well as keywords including egg, egg consumption, cardiovascular disease, cardiovascular events, coronary artery disease, acute myocardial infarct, acute coronary syndrome, stroke, or heart failure. (online supplementary)

**Study selection**

Studies were included in this analysis if the following criteria: the study design was either prospective or cross-sectional, the exposure of interest was egg consumption, the outcome was combined cardiovascular disease events, coronary artery disease, acute myocardial infarct, acute coronary syndrome, stroke or heart failure, and the investigators reported hazard ratios with 95% confidence intervals. Reviews, editorials, non-human studies, letters without sufficient data, studies of other exposures and diseases were excluded.

**Data extraction**

Two reviewers (CK and BN) performed data extraction using a standard extraction form and then review by other reviewers (HH and HZ). Authors, year of publication, study name, study
location, years of follow-up, sample size (number of participants and incident cases), participants’ characteristics (age and sex), endpoints (e.g., coronary artery disease, stroke), outcomes ascertainment, egg consumption categories, covariates adjusted in the multivariable analysis, hazard ratios (95% confidence intervals) for all categories of egg consumption were extracted from included studies. Conflicts were resolved through consensus.

**Quality assessment**

Two independent reviewers performed the quality assessment (BN and HJ) using the Newcastle-Ottawa quality assessment scale, a validated scale for non-randomized studies in meta-analyses. Conflicts were resolved through consensus. We assigned scores of 0-3, 3.5-6, and 6.5-9 for a low, moderate, and high quality of studies, respectively. We consulted dietitians and nutritionists for servings, nutritional units. We contacted the authors if the data of interest were not directly shown in the publications.

**Statistical analysis**

In this meta-analysis, the hazard ratios (HRs) and 95% confidence intervals were considered as the effect size for all studies. Any results stratified by sex were separated as two cohorts. We used the DerSimonian & Laird random-effects method to pool HRs from the included studies. We also conducted subgroup analyses based on sex, study location, number of cases and participants, duration of follow-up, egg consumption measurements, study quality, and whether diet variables or cholesterol levels were controlled for in models. The difference between subgroups was evaluated using the interaction test proposed by Altman. Heterogeneity between studies was measured by $I^2$. Substantial heterogeneity was defined as $I^2 > 50%$. Stata
version 11 (Stata Corp) and R version 3.6.1 were used for statistical analyses. A two-sided p-value of less than 0.05 was considered as statistically significant.

RESULTS

Figure 1 shows the results of literature research and selection. We identified 530 articles from PubMed, SCOPUS, and COCHRANE database from 1966 to January 31, 2020. We identified 23 prospective studies with a median follow-up of 12.28 years. A total of 1,415,839 individuals with a total of 123,660 cases and 157,324 cardiovascular disease events were included. We categorized cardiovascular disease as 94,175 coronary heart disease, 3,112 heart failure, 19,173 acute myocardial infarction, and 40,864 stroke cases. The study population included 565,385 individuals from China, 495,972 from the United States, 10,802 from New Zealand, 166,790 from Japan, 6636 from Finland, 488 from Australia, 14,185 from Spain, 702 from Lithuania, 65,364 from France, 26,930 from Sweden, 9248 from Korea, 1781 from the UK, 7216 from Mediterranean countries, 14337 from the Middle East, 6282 from Africa and 23,721 from South America.

We did not find a significant association between egg consumption and increased risk of overall cardiovascular disease events (HR, 0.99; 95% CI, 0.93-1.06; $I^2=72.1\%$). (Figure 2) Compared to the consumption of no or 1 egg/day, higher egg consumption (more than 1 egg/day) was associated with a significantly decreased risk of coronary artery disease (HR, 0.89; 95% CI, 0.86-0.93; $I^2=0\%$). (Figure 3); however, higher egg consumption (more than 1 egg/day) was not associated with the risk of stroke (HR, 0.92; 95% CI, 0.84-1.02; $I^2=60.1\%$). (Figure 4) In subgroup analyses using study type (prospective vs. retrospective), geography, and follow up year, we did not find any associations between egg consumption and risk of cardiovascular disease. There was no significant difference between the subgroups. After excluding studies with
a moderate risk of bias, we did not find any associations between egg consumption and risk of cardiovascular disease.

**DISCUSSION**

The present meta-analysis, including studies from 1966 to 2020, identified no significant association between egg consumption and risk of cardiovascular disease events, but we found that egg consumption (> 1 egg per day) is associated with a reduction in coronary artery disease risk. Similarly, the previous meta-analysis of 8 observational studies showed no significant association between egg intake and cardiovascular disease events. (10) However, there is substantial heterogeneity in that meta-analysis due to adjusted variables in included studies. A recent meta-analysis found moderate egg consumption (< 1 egg per day) is not associated with cardiovascular disease risk overall. (11) These results are consistent with a subgroup analysis of our study. From evidence to date, either 1 egg or more than 1 egg consumption is not associated with cardiovascular disease. Another meta-analysis of overall dietary cholesterol, including eggs, found no significant either coronary artery disease or stroke risks. (12) However, those included studies in that meta-analysis were heterogeneous and lacked the methodologic rigor to draw any conclusions. To date, studies of egg consumption and coronary artery disease, including meta-analyses, have been inconsistent. The latest meta-analysis of intake of 12 major food groups, including eggs, suggested an optimal eggs consumption may lower risk of coronary artery disease. (13) Previous meta-analysis included 7 prospective studies found no significant association with coronary artery disease by comparing high versus low egg consumption (RR 0.97, 95% CI 0.88 to 1.07). (14) However, the results may be confounded by the inclusion of diabetic patients who have higher cardiovascular disease risks due to dietary patterns than non-
Another meta-analysis of 9 prospective studies reported that egg consumption was not associated with an increased risk of coronary artery disease but was associated with a significantly elevated risk of coronary artery disease in diabetic populations. (10) Interestingly, our study found no association between egg consumption and coronary artery disease in both diabetic groups and non-diabetes groups.

Egg consumption may reduce coronary artery disease via a mechanism of promoted carotenoid absorption (16, 17), enhanced HDL cholesterol function (18, 19), increased bioactive compounds (e.g., lutein and zeaxanthin), resulting in protecting against atherosclerosis. (20) The discrepancy of previous studies may be due to small sample sizes, a lack of adjustment for overall dietary pattern, ethnic difference, and only adjusting for blood glucose instead of excluding diabetic patients. For example, a recent meta-analysis found that egg consumption up to one egg per day is probably associated with a slightly lower cardiovascular disease risk among Asians. (21) Most importantly, Individuals who consume egg may consume processed meats or bacon or high salt intake.

There are certain limitations to our meta-analysis. First, participants may have changed their dietary pattern during the long follow-up period, particularly in the US (e.g., the change in recommendation from the Dietary Guidelines for Americans 2015–2020). Second, self-reported diet data could potentially lead to measurement errors. Third, the statistical power was limited in subgroup analyses of subtypes of stroke (ischemic vs. hemorrhagic) or heart failure (heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction). Forth, dietary data collection with food frequency questionnaires inevitably leads to some measurement errors. Finally, the study findings are observational and cannot establish causality.
In conclusion, our analysis suggests that higher consumption of eggs (more than 1 egg/day) was not associated with increased risk of cardiovascular disease, but a reduction in risk of coronary artery disease.

**CRediT author statement**

**Krittanawong**: Conceptualization, Methodology, Software, Data extraction, Writing- Original draft preparation; **Narasimhan**: Data curation, Data extraction, Writing- Original draft preparation; **Virk**: Data extraction, Data curation, Reviewing and Editing; **Wang**: Statistical analyses and validation; **Farrell**: Data extraction; **Zhang**: Data extraction, Data curation; **Tang**: Supervision, Reviewing and Editing
REFERENCES


FIGURE LEGENDS

**Figure 1**: Study design. This flow chart illustrates the selection process for published reports.

**Figure 2**: Hazard ratio of cardiovascular diseases associated with egg consumption (more than 1 egg/day vs. no/1 egg/day).

**Figure 3**: Hazard ratio of coronary artery disease associated with egg consumption (more than 1 egg/day vs. no/1 egg/day).

**Figure 4**: Hazard ratio of stroke associated with egg consumption (more than 1 egg/day vs. no/1 egg/day).
Figure 1: Study design. This flow chart illustrates the selection process for published reports.

- 530 references imported for screening
- 38 full-text studies assessed for eligibility
- 27 selected studies
- 492 irrelevant studies
- 11 studies insufficient data
Figure 2: Hazard ratio of cardiovascular diseases associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)
Figure 3: Hazard ratio of coronary artery disease associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)
**Figure 4:** Hazard ratio of stroke associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)
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Note: FFQ = Food Frequency Questionnaire; ICD = International Classification of Diseases; DM = Diabetes Mellitus; HTN = Hypertension; HLD = Hyperlipidemia; FH = Family History; CV = Cardiovascular; WHR = Waist-to-Hip Ratio; MI = Myocardial Infarction; T2DM = Type 2 Diabetes Mellitus; M = Male; F = Female; M = Mediterranean; Pictsort = Picture-sort; Interview administered questionnaire.
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Meat, fish, vegetables, fruits, and cohort effects.